REMARKS

Claims 14, 22, and 25-27 have been amended to further clarify the invention. Claim 24 has been canceled. Claim 45 is newly presented. After entry of the amendment, claims 14-23, 25-30, and 45 are pending. Claims 1-8, 10-12, and 14-44 remain pending in this application. Favorable reconsideration is respectfully requested in light of the amendments and remarks submitted herein.

Applicants submit the amendments to the claims and newly presented claim are supported throughout the specification, including at page 8, lines 10-16 and Example 3 beginning at page 14, line 14, and do not raise any issues of new matter.

Enablement

The Examiner objected to the specification and rejected claims 14-24, 28, and 29 under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention. Applicants respectfully traverse the objection to the specification and rejection of claims.

The Examiner asserts the examples are neither exhaustive nor define the class of compounds and states the "the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity." Applicants strongly disagree.

The standard for enablement is met if the disclosure reasonably apprises the ordinary artisan, in light of what is well-known in the art, how to make and how to use a claimed invention throughout its scope. MPEP § 2164.08. The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts a disclosure of every operable species is not required. MPEP § 2164.03.

Applicants have directed the claims to cholinesterase and/or carboxylesterase inhibitors. The specification and working example define the class of compounds required. Applicants teach that cholinesterase and carboxylesterase are important for metabolism of aryl phosphate derivatives of d4T and that inhibiting cholinesterase and/or carboxylesterase significantly extends the half-life of aryl phosphate derivatives of d4T in plasma. See, for example, the specification at page 8, lines 10-16 and Table 1 in Example 3. Applicants have described specific cholinesterase and carboxylesterase inhibitors and described and provided a working

example of extending the half-life of an aryl phosphate derivative of d4T with a cholinesterase and/or carboxylesterase inhibitor.

Based on Applicants' teachings, one skilled in the art would expect that the claimed genus of cholinesterase and/or carboxylesterase inhibitors could be used in the claimed method without undue experimentation. The level of skill in the art is high. At the time of invention, inhibitors of cholinesterase and/or carboxylesterase were well known in the art. See, for example, E. Giacobini, 2000, *Alzheimer Dis. Assoc. Disorders*, 14:S3-S10 (copy enclosed), D. Knopman, 1998, *Geriatrics*, 53:S31-S34 (copy enclosed), Iley et al., 1999, *Eur. J. Pharm. Sci.*, 9:210-205 (abstract enclosed), Dettbarn et al., 1999, *Chem. Biol. Interact.*, 119-120:445-454 (abstract enclosed), and Bogdanffy et al., 1999, *Inhal. Toxicol.*, 11:927-941 (abstract enclosed). The specification describes a method for quantitative HPLC detection of aryl phosphate derivatives of d4T and their metabolites and describes a method to determine the stability of aryl phosphate derivatives of d4T in whole blood and plasma and plasma supplemented with known inhibitors of cholinesterase and carboxylesterase. See, for example, Example 1 beginning at page 13, line 10, Example 2 beginning at page 14, line , and Example 3 beginning at page 14, line. In view of Applicants' teachings, one skilled in the art would have expected that any inhibitor of cholinesterase and/or carboxylesterase could be used in the claimed method to extend the half-life of an aryl phosphate derivative of d4T in plasma.

Even if some of the inhibitors in the claimed genus of cholinesterase and/or carboxylesterase inhibitors were inoperative, the claims are not necessarily rendered nonenabled. *Atlas Powder v. E.I. Du Pont De Nemours*, 750 F.2d 1569, 1576. Inoperative embodiments do not render a claim nonenabled if a person skilled in the art could determine which embodiments that were conceived but not yet made would be operative or inoperative with expenditure of no more effort than is normally required in the art. *Atlas Powder*, 750 F.2d at 1576. In view of Applicants' examples, one skilled in the art would have been able to determine which embodiments are operative or inoperative without undue experimentation. Moreover, at the time of invention, the structure of cholinesterase and the mode of action of many cholinesterase inhibitors were well known. Imbimbo, 2001, *CNS Drugs*, 15:375-390 (copy enclosed). Therefore, one skilled in the art would have been able to select operative embodiments from the genus of cholinesterase inhibitors based on the mode of action of the cholinesterase inhibitors used in Applicants' examples.

In view of the forgoing, Applicants assert one skilled in the art would be able to make and use the claimed invention without undue experimentation. Withdrawal of the objection to the specification and rejection of claims is respectfully requested.

Indefiniteness

The Examiner rejected claims 14-24, 28, and 29 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection.

Applicants have directed the claims to an esterase inhibitor, wherein the esterase inhibitor is a cholinesterase inhibitor, carboxylesterase inhibitor, or a combination of cholinesterase and carboxylesterase inhibitors. The specification describes specific examples of cholinesterase and carboxylesterase inhibitors. Moreover, at the time of invention, inhibitors of cholinesterase and/or carboxylesterase were well known in the art. See, for example, E. Giacobini, 2000, *Alzheimer Dis. Assoc. Disorders*, 14:S3-S10 (copy enclosed), D. Knopman, 1998, *Geriatrics*, 53:S31-S34 (copy enclosed), Iley et al., 1999, *Eur. J. Pharm. Sci.*, 9:210-205 (abstract enclosed), Dettbarn et al., 1999, *Chem. Biol. Interact.*, 119-120:445-454 (abstract enclosed), and Bogdanffy et al., 1999, *Inhal. Toxicol.*, 11:927-941 (abstract enclosed).

Applicants submit the objected to phrase clearly defines the subject matter within the scope of Applicants' claims. Withdrawal of the rejection is respectfully requested.

Novelty

The Examiner rejected claims 14-24, 28, and 29 under 35 U.S.C. § 102(b) as being anticipated by McGuigan et al., 1998, *Antiviral Chem. Chemother.*, 9:109-115 or Perigaud et al., 1996, *Antiviral Ther.*, 1(Suppl. 4):39-46. Applicants respectfully traverse this rejection.

To anticipate a claim, each and every element of the claim must be described, either expressly or inherently, in a single prior art reference. *Verdegaal Bros. v. Union Oil*, 814 F.2d 628, 631 (Fed. Cir. 1987). McGuigan et al. does not disclose a compound that falls within the scope of Applicants' claims. The aryl group in the compounds disclosed by McGuigan et al. is unsubstituted. In contrast, Applicants claims require the aryl group be substituted with an electron withdrawing group. Therefore, the compounds disclosed in McGuigan et al. do not expressly or inherently anticipate Applicants' claims.

Perigaud et al. does not specifically disclose a compound that falls within the scope of Applicants' claims. Perigaud et al. specifically discloses ddA and d4T. Neither ddA nor d4T have an aryl group substituted with an electron withdrawing group, as required by Applicants' claims. Therefore, the compounds disclosed in Perigaud et al. do not expressly or inherently anticipate Applicants' claims.

In view of the forgoing, Applicants respectfully request withdrawal of the rejection.

Obviousness

The Examiner rejected claims 14-30 under 35 U.S.C. § 103(a) as being unpatentable over McGuigan et al. and Perigaud et al. in view of Vahlquist, 1935, 30CA:856 and Keller, 1963, 62CA:3881e-h. Applicants respectfully traverse this rejection.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP § 2142. Three criteria must be met by the Examiner to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has failed, in the least, to establish that the cited references teach or suggest all of the limitations of the claims.

As discussed above, neither McGuigan et al. nor Perigaud et al. teach or suggest a compound that falls within the scope of Applicants' claims. Neither Vahlquist nor Keller, alone or in combination, cure the deficiencies of the primary references. Neither Vahlquist nor Keller teach or suggest substituting the aryl group of the compounds disclosed in McGuigan et al. or Perigaud et al. with an electron withdrawing group. Moreover, none of the references cited by the Examiner, alone or in combination, teach or suggest administering an inhibitor of cholinesterase and/or carboxylesterase to extend the half-life of the aryl phosphate derivatives of d4T of Applicants' claims. Therefore, the Examiner has failed to establish that the cited references teach or suggest all of the limitations of the claims.

In view of the forgoing, Applicants assert the Examiner has failed to establish a *prima facie* case of obviousness. Withdrawal of the rejection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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